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Thyroid function tests in type 1 diabetes mellitus in Al-Najaf governorate

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Abstract

Background: Clinically, diabetes and thyroid illnesses are the most frequent endocrine disorders. Longstanding links have been found between thyroid problems and type 1 diabetes mellitus. To some extent, type 1 Diabetes mellitus impacts thyroid function testing, although thyroid hormones regulate carbohydrate metabolism and pancreatic function.

Objectives: To assess thyroid function in type 1 Diabetes Mellitus patients as part of autoimmune association.

Method: A case-control study. The study included 50 children with T1DM (27 males and 23 female) aged 7.20 ± 1.53 (4-10) years. The average diabetes duration was 2.84 ± 1.46 years. The study comprised 50 children (25 males and 25 female) aged 6.32 ± 1.39 (4-10) years as normal controls. Blood glucose, thyroid stimulating hormone (TSH), total thyroxine (TT4), total triiodothyronine (TT3), and growth parameters (weight and height) are examined in T1DM patients to determine the cause of thyroid hormone dysfunction. Mini Vidas immunoassay analyzer with Enzyme Linked Fluorescence Assay (ELFA) measures TSH, TT4 and TT3 levels, while Glucometer (ACCU-CHEK® Active) measures blood glucose.

Results: In a study comparing thyroid function among Type 1 Diabetes Mellitus (T1DM) patients and non-diabetic controls, significant alterations were observed in T1DM patients, with 18% exhibiting elevated TSH levels and 6% showing reduced TT3 levels. Further subgroup analysis revealed notable differences based on diabetic ketoacidosis (DKA) episodes, insulin therapy regularity, frequency of diabetes clinic visits, and the presence of chronic diseases like asthma and celiac disease. Specifically, irregular insulin therapy, infrequent clinic visits, and the presence of chronic diseases were associated with higher TSH and lower TT3 concentrations, highlighting the impact of diabetes management and comorbid conditions on thyroid function in T1DM patients.

Conclusion: Our findings suggest that type I diabetics without clinical symptoms may benefit from TSH and TT3 measurement to detect thyroid impairment early.

Keywords: Thyroid, function, tests, type 1 diabetes mellitus, AL-Najaf governorate

1. Introduction

Diabetes Mellitus (DM) is defined by the WHO as a metabolic disorder characterized by chronic hyperglycemia due to defects in insulin secretion, action, or both, leading to disturbances in carbohydrate, fat, and protein metabolism. It encompasses a spectrum of diseases, including Type 1 Diabetes Mellitus (T1DM), which results from pancreatic β -cell damage, and Type 2 Diabetes Mellitus (T2DM), stemming from insulin resistance and varying degrees of β -cell impairment. Insulin, a crucial metabolic hormone produced by the pancreas, facilitates glucose uptake, glycogen and triglyceride synthesis, and inhibits lipolysis and gluconeogenesis. Exogenous insulin types are classified by their action times and often combined in therapy to mimic natural insulin activity^[1-2]. T1DM, formerly known as insulin-dependent diabetes, primarily affects children and adolescents, necessitating lifelong exogenous insulin use to prevent ketoacidosis. Its rising incidence, particularly at younger ages, reflects a complex interplay of genetic predisposition, autoimmunity, and environmental factors. Genetic susceptibility is significant, with familial clustering observed and the major histocompatibility complex on chromosome 6 playing a crucial role. However, environmental triggers, such as viral infections and dietary factors, are essential for disease manifestation^[3-4]. The pathogenesis of T1DM involves T-cell mediated autoimmune destruction of β -cells, with disease progression marked by stages from autoimmunity initiation to established diabetes and complications, including both acute and chronic

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manifestations. Diagnosis relies on symptoms like polyuria and confirmed by elevated blood glucose levels or hemoglobin A1C [5-6]. The thyroid gland, critical for growth and metabolic regulation, develops from the pharyngeal gut and functions independently from mid-gestation. Thyroid hormones, regulated by TSH and iodide, play pivotal roles in somatic and CNS development, with dysfunctions diagnosable through thyroid function tests (TFTs). T1DM patients frequently encounter autoimmune thyroid disease (ATD), with a notable prevalence compared to T2DM subjects, affecting glucose metabolism and necessitating periodic monitoring [7-8]. The aim of this study is to assess thyroid function in children with type 1 diabetes mellitus as part of autoimmune associated dysfunctions.

Methods

A case-control study was conducted at the Department of Pediatrics, Al-Zahraa Teaching Hospital, Al-Najaf Al-Ashraf city, from May 2012 to January 2013. The study included 50 patients diagnosed with Type 1 Diabetes Mellitus (T1DM) from Al-Najaf Center for Diabetes and Endocrine in Al-Sadir and Al-Zahraa teaching hospitals. These patients, aged 4-10 years, were taking insulin for glucose control, with a gender distribution of 27 males and 23 females, residing in both urban (28) and rural (22) areas. A clinical history and physical examination were performed to exclude thyroid diseases. Among these patients, 16 had asthma, 4 had celiac disease, and 30 had no chronic diseases. Family history revealed 7 cases of DM, including 1 with T1DM and 6 with T2DM. Data on insulin type, episodes of Diabetic Ketoacidosis (DKA), treatment regularity, and clinic visits were collected. The control group comprised 50 healthy children, relatives of inpatients and outpatients at Al-Zahraa Teaching Hospital, residing in the same geographical area with an equal distribution of rural and urban residents. They were matched with the diabetic children by sex and age, with a similar profile of chronic diseases and family history of DM. Inclusion criteria for the diabetic group required a T1 DM diagnosis and insulin treatment for glucose control. Exclusion criteria

included severe complications of DM, any thyroid disease, recent acute illness, and medications affecting thyroid function. Three subjects were excluded due to hemolyzed samples. Blood samples (5 ml) were collected from each participant, centrifuged to obtain serum, and analyzed for TSH, TT4, and TT3 using VIDAS Kits and a Mini VIDAS instrument through an enzyme immunoassay method with fluorescent detection. Random blood glucose levels were measured using an ACCU-CHEK® Active glucometer, with test strips analyzed in 5 to 10 seconds for glucose concentration. Statistical analysis was performed using SPSS-18, presenting data in frequencies, percentages, means, and standard deviations. The significance of mean differences between T1DM and control groups was assessed using ANOVA, with p-values < 0.05 indicating statistical significance, < 0.01 high significance, and < 0.001 extreme significance. This study aimed to understand the biochemical parameters and health status of children with T1DM compared to healthy controls in Al-Najaf, contributing valuable insights into the condition's management and impact on pediatric populations.

Results

The group of 50 cases and 50 controls (final case-to-control ratio 1:1) was selected from 51 potential patients and 52 potential controls. The study removed three participants (1 case, 2 controls) due to sample hemolysis. TSH levels in type 1 diabetes patients and controls were 4.05 ± 1.98 mIU/L (9 (18%) elevated) and 2.29 ± 0.87 mIU/L (all normal). A significant difference ($p < 0.008$) was seen in TSH levels between patients and controls. The mean \pm SD TT3 concentrations in type 1 diabetes patients and controls were 1.82 ± 0.35 mIU/L (6% lowered) and 2.16 ± 0.43 mIU/L (all normal). There was a significant difference ($p < 0.01$) in TT3 values between patients and controls, but no significant difference ($p = 0.15$) in TT4 values between type 1 diabetic patients (103.38 ± 8.4 mIU/L) and controls (109.70 ± 6.72 mIU/L) (see figure (1) and table (1)).

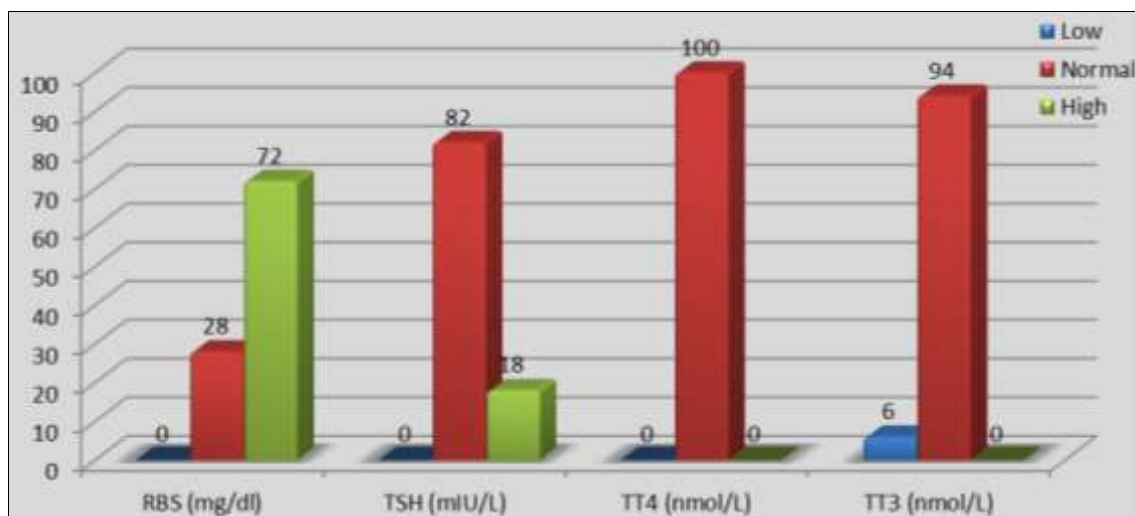


Fig 1: The percentage of normal and abnormal value of RBS, TSH, TT4 and TT3 in diabetic group.

Table 1: Distribution of RBS, TSH, TT4 and TT3 in T1DM patients and normal control.

		Diabetics		Controls		Diabetics	Controls	P value
		No.	%	No.	%			
RBS (mg/dl)	Low	-	-	-	-	166.99±61.78 (88.5-310.0)	92.41±8.15 (78.5-112.0)	0.001**
	Normal < 200	14	28.0	50	100			
	High	36	72.0	-	-			
TSH (mIU/L)	Low	-	-	-	-	4.05±1.98 (0.96 -8.12)	2.29±0.87 (1.0 4.2)	0.008**
	Normal (0.25-5)	41	82.0	50	100			
	High	9	18.0	-	-			
TT4 (nmol/L)	Low	-	-	-	-	103.38±8.4 (88.2-119.8)	109.70±6.72 (93.1-119.9)	0.55
	Normal (60-120)	50	100.0	50	100			
	High	-	-	-	-			
TT3 (nmol/L)	Low	3	6.0	-	-	1.82±0.35 (0.74 -2.78)	2.16±0.43 (1.58-3.19)	0.01*
	Normal (0.92- 2.33)	47	94.0	50	100			
	High	-	-	-	-			

Data were presented as Mean±SD (Range).

*Significant using Students-t-test for two independent means at 0.05 levels of significance.

Table 2: Growth parameters measurements in diabetics and controls. Results are presented as median (range).

	Diabetics	Controls	P value
Weight (Kg)	22.01±5.19(14.3-34.5)	21.12±3.72(15.5-36.8)	0.26
Height (cm)	115.86±8.69 (93.5-134.5)	113.77±10.03 (92.4-133.5)	0.309

-Data were presented as Mean±SD (Range)

*Significant using Students-t-test for two independent means at 0.05 levels.

Table 3: Distribution of TSH, TT4 and TT3 in T1DM patients group according to age and sex.

	No.	TSH (mIU/L)	TT4 (nmol/L)	TT3 (nmol/L)	
Age (years)	4	1	3.4±	97.1±	2.2±
	5	5	4.0±2.16	100.2±4.60	2.0±0.09
	6	12	4.6±2.41	100.1±6.37	1.8±0.18
	7	13	3.7±1.90	104.2±16.82	1.8±0.46
	8	7	3.9±1.81	101.7±6.75	1.8±0.15
	9	8	4.4±2.88	100.8±8.17	1.7±0.31
	10	4	5.6±1.72	99.6±6.19	2.0±0.31
	P value		0.800	0.960	0.463
Sex	Male	27	4.0±2.07 (3/50=5.55%)	99.2±5.54	1.9±0.22
	Female	23	4.5±2.26 (6/50=13.04%)	104.0±13.23	1.8±0.38
		P value		0.384	0.089

-Data were presented as Mean±SD

*Significant using ANOVA test for difference among three means and more or Students-t-test for difference between two independent means at 0.05 level.

Table 4: Distribution of TSH, TT4 andTT3 in T1DM patients group according to residence, educational status and duration of disease (years).

	No.	TSH (mIU/L)	TT4 (nmol/L)	TT3 (nmol/L)	
Residence	Urban	28	3.9±2.10	103.5±11.70	1.8±0.29
	Rural	22	4.5±2.21	99.3±7.74	1.9±0.32
		P value		0.315	0.144
Educational status	No	15	4.0±2.14	99.4±5.63	1.9±0.20
	First class	16	4.1±2.13	103.9±15.20	1.8±0.42
	Second class	8	4.5±2.37	101.2±6.44	1.7±0.16
	Third class	7	3.8±2.51	101.3±8.70	1.8±0.32
	Fourth class	1	6.8±	100.4±	1.6±
	Fifth class	3	5.2±1.84	99.4±7.56	2.1±0.17
	P value		0.780	0.895	0.317
Duration of disease (years)	1	8	3.2±0.75	104.2±7.28	2.0±0.15
	2	18	4.6±2.54	99.4±6.54	1.9±0.37
	3	10	3.7±1.63	106.8±6.13	1.8±0.28
	4	5	3.8±2.21	99.1±12.91	1.7±0.38
	5	6	6.0±2.36	96.1±3.12	1.8±0.31
	6	3	3.6±2.10	102.7±8.93	1.9±0.16
		P value		0.189	0.288

-Data were presented as Mean±SD

*Significant using ANOVA test for difference among three means and more or Students-t-test for difference between two independent means at 0.05 level.

Mean±SD measurements of weight (22.01±5.19 kg) and height (115.86±8.69 cm) in the type 1 diabetic patients and in the control subjects (21.12±3.72 kg) and (113.77±10.03 cm) respectively. No significant differences between diabetic patients and the control groups in weight (p=0.26) and height (p=0.309) respectively as shown in (Table 2). No significant differences of TSH, TT4 and TT3 concentrations in the type 1 diabetic patients group in age (p=0.8, 0.96 and 0.46) and sex (p=0.38, 0.89 and 0.08) respectively were found (Table 3). No significant differences of TSH, TT4 and TT3 concentrations in the type 1 diabetic patients group according to residency [21rural and 28urban areas (p=

0.315, 0.144 and 0.483)], educational status (p=0.78, 0.895 and 0.317) and duration of diabetic disease (p=0.189, 0.288 and 0.636) respectively as shown in table (8). Thirty-nine diabetic patients had a history of DKA, while eleven did not. The mean±SD concentrations of TSH, TT4, and TT3 were analyzed, with significant differences in TSH (9/39, 23.1%) increased significantly (p< 0.0001) and TT3 con. Table 5 shows that patients with irregular insulin therapy (38/50) had higher TSH concentrations (23.68%) compared to those with regular insulin therapy (12/50). However, there were no significant differences in TT4 or TT3 concentrations.

Table 5: Comparison of TSH, TT4, and TT3 in diabetic group according to DKA episodes and insulin therapy administration.

		No.	TSH (mIU/L)	TT4 (nmol/L)	TT3 (nmol/L)
DKA episodes	No	11	2.7±1.06	104.8±16.88	1.9±0.20
	One	15	3.8±1.42	103.8±7.02	2.1±0.22
	Two	15	4.1±2.26	99.4±6.56	1.7±0.34
	Three	9	7.0±1.48	96.6±6.34	1.6±0.24
	P value		0.0001*	0.193	0.0001*
Insulin therapy administration	Good control	12	2.7±1.06	104.8±16.88	1.9±0.20
	irregular treatment	38	4.8±2.17	100.1±7.27	1.9±0.32
	P value		0.008*	0.510	0.148

-Data were presented as Mean±SD

*Significant using ANOVA test for difference among three means and more or Students-t-test for difference between two independent means at 0.05 level.

No significant differences of TSH, TT4 and TT3 concentrations in the type 1 diabetic patients group according to insulin type (32/50 mixture and 18/50 lente -

soluble); (p=0.599, 0.132 and 0.571 respectively) and daily insulin requirement (u/kg/day) (p=0.267, 0.825 and 0.085) respectively as shown in table (6).

Table 6: Comparison of TSH, TT4, and TT3 in diabetic group according to insulin type and insulin therapy requirement (u/kg/day).

		No.	TSH (mIU/L)	TT4 (nmol/L)	TT3 (nmol/L)
Insulin type	Mixture	32	4.1±2.12	103.0±10.93	1.8±0.27
	L/S	18	4.4±2.27	98.5±7.69	1.9±0.37
	P value		0.599	0.132	0.571
Insulin requirement (u/kg/day)	15--	7	3.1±2.33	97.9±3.57	1.9±0.19
	20--	19	4.2±2.07	103.6±13.15	1.9±0.23
	25--	10	3.8±1.72	100.3±9.18	1.8±0.33
	30--	8	4.4±2.13	102.4±8.91	1.9±0.38
	35--	4	6.4±0.77	98.6±7.92	1.6±0.40
	=>40	2	4.9±5.30	100.6±4.56	1.3±0.26
	P value		0.267	0.825	0.085

-Data were presented as Mean±SD

*Significant using ANOVA test for difference among three means and more or Students-t-test for difference between two independent means at 0.05 level.

Table 7: Comparison of TSH, TT4, and TT3 in diabetic group according to regular visit to DM Clinic, family history of DM and Associated with chronic diseases.

		No.	TSH (mIU/L)	TT4 (nmol/L)	TT3 (nmol/L)
Regular visit to DM Clinic	Regular	28	3.1±1.29	104.9±11.07	1.9±0.27
	Irregular	22	5.7±2.18	97.0±6.48	1.7±0.30
	P value		0.0001**	0.066	0.005**
Family history of DM	T2DM	6	4.1±1.59	102.4±8.18	1.9±0.14
	T1DM	1	3.7±	114.3±	2.0±
	No	43	4.2±2.26	101.0±10.27	1.8±0.33
	P value		0.969	0.420	0.829
Associated with chronic diseases	Asthma	16	4.6±2.40	97.9±7.05	1.7±0.37
	Celiac	4	7.8±0.55	95.9±2.38	1.7±0.23
	No	30	3.5±1.56	104.0±11.23	1.9±0.24
	P value		0.001*	0.073	0.024*

-Data were presented as Mean±SD

*Significant using ANOVA test for difference among three means and more or Students-t-test for difference between two independent means at 0.05 level.

Diabetic children were divided into two groups based on regular DM clinic visits (28/50 regular and 22/50 irregular). TSH concentration (5.7 ± 2.18) was significantly higher ($p < 0.0001$) and TT3 concentration (1.7 ± 0.30) was lower ($p < 0.005$) in children with irregular visits, while TT4 concentration was not significantly different. In diabetics, chronic illnesses included asthma (16/50) and celiac (4/50). TSH (7/20, 35%) was significantly higher ($p < 0.001$) than diabetic patients without chronic disease (2/30), TT3 (3/20, 15%) was lower ($p < 0.024$), and TT4 ($p = 0.073$) was not significantly different. Table (7) shows that type 1 diabetics with family histories of DM had similar TSH, TT4, and TT3 values.

Discussions

In our study, we observed significantly higher serum Thyroid-Stimulating Hormone (TSH) levels in patients with Type 1 Diabetes Mellitus (T1DM) compared to non-diabetic controls ($p < 0.008$), with 18% of the T1DM patients showing elevated TSH concentrations. This finding aligns with previous studies, such as Cardoso *et al.* (1995) [19], who reported subclinical hypothyroidism in 21% of T1DM patients in Africans, and A. Ditta *et al.* (2001) [10], who found significantly elevated serum TSH levels in T1DM patients compared to controls, with 30% of diabetic patients showing elevated TSH. Umpierrez *et al.* (2003) [11] highlighted a 2-to-3 fold increased risk of thyroid dysfunction in T1DM patients over the general population, noting higher hypothyroidism rates in females. Similarly, Soliman GZA *et al.* (2012) [12] reported subclinical hypothyroidism prevalence of 11.2% in T1DM children, underscoring the potential for coexisting autoimmune conditions affecting the pancreas and thyroid. Contrarily, Palanisamy *et al.* (2008) [13] found lower TSH levels in diabetics, attributing this to decreased Thyrotropin-Releasing Hormone (TRH) synthesis in diabetes. Our study revealed a higher prevalence of subclinical hypothyroidism in female diabetic patients compared to males, although not statistically significant. This observation is consistent with studies indicating a higher incidence of thyroid dysfunction among females with diabetes [14-15], potentially linked to the higher prevalence of obesity in female diabetics and the impact of insulin and C-peptide on TSH turnover. Regarding Triiodothyronine (TT3) levels, we found a significant reduction in T1DM children compared to controls ($p < 0.01$), which could be due to inhibited hepatic conversion of Thyroxine (T4) to TT3, as insulin suppresses TT3 levels by affecting this conversion process [16-17]. However, Thyroxine (TT4) levels in our study were not significantly different from controls, contrasting with A. Ditta *et al.* (2001) [10], who observed decreased TT4 concentrations in T1DM patients. We also analyzed TSH, TT4, and TT3 concentrations in relation to the duration of diabetic disease, finding no significant differences. However, elevated TSH was noted in children with ≥ 5 years of diabetes, suggesting a correlation with autoimmune thyroid disease (ATD), which is more prevalent in T1DM patients due to common autoimmune mechanisms [18]. This association strengthens with the duration of diabetes, as indicated by Faranak Sharifi *et al.* [19], who found a positive correlation between diabetes duration and anti-thyroid peroxidase antibody titers. Subgroup analyses revealed significant differences in TSH and TT3 levels among diabetic children with a history of Diabetic Ketoacidosis

(DKA) episodes and those with irregular insulin therapy or clinic visits, indicating that these factors may exacerbate thyroid dysfunction in T1DM patients [20-21]. Furthermore, diabetic patients with chronic diseases like asthma and celiac disease exhibited significantly altered TSH and TT3 levels, highlighting the interconnectedness of autoimmune conditions in T1DM [22-23].

Conclusion

Our study revealed thyroid dysfunctions in type 1 diabetic children (high percentage of the estimation of TSH and a lesser degree TT3) and this may be useful in early identification of thyroid dysfunction in T1DM patients without any clinical signs of thyroid disease.

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